The Effect of Expectation on Response to Phenmetrazine

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To investigate the effect of expectation on response to an appetite-depressing drug, 50 experiments were carried out upon 4 healthy subjects of average weight. In all experiments, after a 5-hr. fast, subjects were given either phenmetrazine 25 mg. p.o., or a matching placebo 30 min. prior to a test meal. A sham experiment was carried out to disguise the purpose of the study. In 28 experiments subjects were told nothing about the drugs and consumed a mean of 1860 ± 265 calories following phenmetrazine, as compared to 1900 ± 172 calories following the placebo ($p > .50$). In the 22 ensuing experiments, subjects were told that appetite depression might occur. With this expectation, subjects receiving phenmetrazine consumed 1770 ± 82 calories, compared with a placebo mean of 1950 ± 141 calories ($p < .01$). In these experiments, the effect of phenmetrazine on food intake was greatly enhanced when subjects knew that they might receive an appetite-depressing drug.

IT IS WELL ACCEPTED that the response of a person to an agent which is expected to modify his mood, thought, or behavior may be altered by changing his expectation of the effect of the drug. It is also true that if suggestion is used, inert substances may exert a powerful effect upon susceptible individuals, and the effect of active drugs upon them may be greatly modified. However, these two phenomena may not be entirely similar in their mechanism. The effect of anticipation on the action of drugs may not be simply a "placebo response." It may reflect, rather, an improvement in the subject's ability to discriminate the effect of drugs from those of placebos.

The series of experiments reported here was designed to test the effect of expectation on response to phenmetrazine, a widely used appetite-depressing drug in the amphetamine series.[1] This drug has gained acceptance in the short-term adjunctive therapy of obesity because it exerts an appetite-depressing effect with minimal side effects.[2] Its site of action is thought to be the cortex.[3]

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Materials and Methods

Subjects for these experiments were 4 healthy young men of normal weight. Experiments were conducted twice weekly at the time of the evening meal. Subjects were asked to eat the same lunch on each experi-

mental day and to eat nothing for at least 5 hr. prior to the experiment. In order to disguise the actual purpose of the experiment, a sham experiment was carried out. Subjects were told that we wished to observe "carotid-pulse volume" under three conditions: (1) fasting without medication; (2) fasting following medication; (3) postprandially, following medication. Carotid pulse was recorded by means of a cup which was held over the carotid artery and attached to a polygraph by a simple pressure transducer. In order to distract the subject's attention from the purpose of the experiment, records were obtained on arrival, 30 min. after medication, and following the meal. Medication was administered 30 min. after the initial recording. Either phenmetrazine, 25 mg., or a matching placebo was given by mouth. Administration was double-blind, and the schedule was randomized so that on any given day, some subjects were given placebo and some were given drug. Thirty minutes following medication, another record was obtained and the test meal was served. The meal contained 2000 calories and consisted of cold roast beef, potato salad, cole slaw, bread and butter, milk and cookies. Food was obtained from the same source on each occasion, and was carefully weighed before serving. Subjects were told that they did not have to finish the meal. The final record was taken a few minutes after the meal. During the experiment, an open-ended symptom checklist of simple design was given to the subjects every 30 min., and they were told to register their reactions.

Symptom Checklist
- Tremor
- Tired
- Hungry
- Pepped-up
- Not hungry
- Palpitation
- Sleepy
- Nauseated
- Annoyed

In order to disguise the purpose of this checklist, neutral items were included with items designed to assess the subject's degree of hunger and also to indicate possible cardiovascular and central-nervous-system stimulation. Subjects were required to check only those symptoms which they noted, and were not required to answer every question Subjects ate together in pleasant surroundings.

During an initial series of 28 experiments, subjects were given no idea what medications might be involved or whether a placebo might be used. In a later series of 22 experiments, each subject was told by the investigator that one of the drugs was an appetite depressant and that he might notice diminished hunger.

Results

During the first series of experiments —when the subjects were unaware of the purpose of the experiment and of the nature of the drugs—the effect of phenmetrazine on the magnitude of food intake was not significantly different from that of the placebo, although an effect was probably present (Fig. 1). On placebo days, subjects consumed 1900 cal. ± 45 cal.* On phenmetrazine days, subjects consumed 1860 ± 71 calories. The difference between these two means is not significant ($p > 0.5$). In the series of experiments in which subjects were aware that they might receive an appetite-depressing drug, they consumed 1950 ± 24 cal. on placebo days and only 1770 ± 45 cal. on phenmetrazine days. The difference between these two means

*Standard error of the mean.

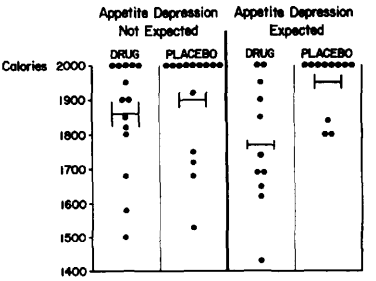

FIG. 1. Effects of drug and placebo on food intake.

is significant at the 1% level. If the data are analysed by χ^2 for completion of the test meal (2000 calories in Fig. 1), the findings suggest that phenmetrazine did exert a small effect upon food intake in the first series of experiments ($p > 10$). A similar analysis applied to the second series of experiments indicates that phenmetrazine had a greater effect ($p < .05$).

The response of the subjects can also be understood in terms of the number of instances in which a subject ate an amount significantly less than his mean control food intake (Fig. 2). Food intake was considered to be significantly depressed when a subject's caloric intake was 3 S.E. less than his mean consumption on placebo days. During the first series of experiments, subjects ate significantly less than their mean control on two of 14 occasions when they received the placebo, and on three of 14 occasions when they received phenmetrazine. Under the conditions obtaining in the second series of experiments, subjects ate significantly less than the mean control on none of 11 occasions when they received the placebo, and on six of 11 occasions when they received phenmetrazine. These results are different at the 1% confidence level (χ^2).

Subjective response to the drug as measured by the symptom checklist was not significantly affected by expectation (Fig. 3). Since there was an entirely open-ended checklist, it was possible for subjects to make no mention of their *degree* of hunger. Responses could therefore be "hungry," "not hungry," "nauseated," or "no mention" of hunger. On placebo days, subjects checked "hungry" eight times, "not hungry" three times, and "no mention" three times. On drug days, subjects checked "hungry" nine times, "not hungry" once, and made no response four times. There is no apparent difference between these responses. In the second series of experiments when subjects were aware

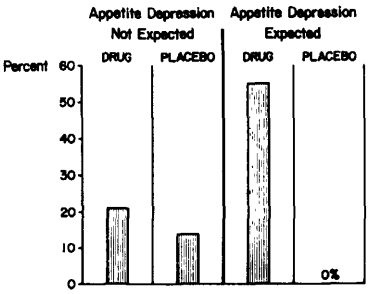

FIG. 2. Depression of food intake.

that they might receive an appetite-depressing drug, subjects checked "not hungry" once, and no mention of hunger was made six times on placebo days. On drug days, "hungry" was checked seven times and no mention was made four times. Again there is no apparent difference between these results. Thus there appears to be no difference between the responses during the first and second series of experiments, whether drug or placebo was administered.

Included in the checklist were items designed to elicit the possible side effects

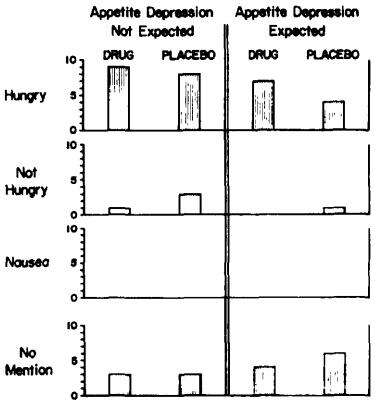

FIG. 3. Subjective hunger responses measured by symptom checklist.

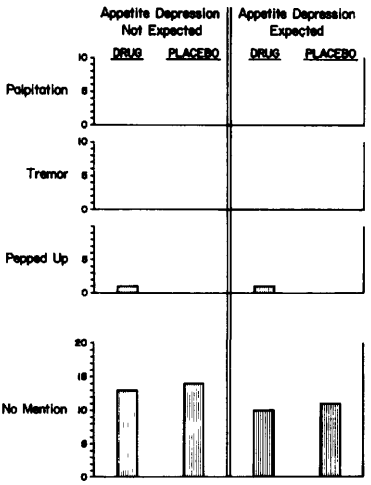

FIG. 4 Side effects as measured by symptom checklist.

of phenmetrazine upon the cardiovascular and central nervous systems (Fig. 4). It is of interest that in the absence of any expectation whatsoever of these effects, only one item, "pepped-up," was checked at all, and that one on only two occasions.

Discussion

In these experiments, the effect of phenmetrazine on food intake was much enhanced when the subject had foreknowledge of the nature of the medication he was to receive. The slight drug effect that was present before subjects had been told that an appetite depressant might be used was significantly enhanced when they had some expectation of appetite depression. It is interesting that this effect on food intake was not mirrored in the symptom checklists. Subjects who ate less seemed to be no less aware of hunger. In the study of appetite-depressing drugs, it is useful to measure more than one aspect of drug effect;[4] it is essential to realize that measurement of different effects may produce quite different results. We have often observed that the statement a subject makes about his degree of hunger and the amount he will eat at a test meal may be greatly at variance. Possibly, in this experiment, the use of a simple open-ended checklist did not provide an adequately sensitive measure of changes in degree of hunger. We purposely avoided more elaborate scales because of the overriding necessity to disguise the purpose of the experiment.

In these experiments, the use of relatively few subjects with a large number of experiments on each individual allowed each subject to serve as his own control, and made it possible to compare drug and placebo on the basis of their effect on each subject's eating behavior over a period of time. However, this plan did introduce the difficulty that the sequence of exposure must always be, first: "no suggestion"; and second: "suggestion," thereby introducing the possibility of systematic bias. Effects of such bias were thought to be: (1) A generally lowered food intake of each subject as the experiment progressed and he became tired of ingesting the same meal repeatedly. (An attempt was made to minimize this by carrying out only two experiments per week and by preparing especially appetizing food.) In fact, food intake in the absence of the drug was slightly greater during the second part of the experiment than the first. This was taken to indicate that the phenomenon of tiring of the test meal did not account for reduced food intake associated with drug administration in the second part of the experiment. (2) Tachyphylaxis. Since it has been observed of phenmetrazine that it tends to lose effect with repeated administration,[3] it is unlikely that increasing susceptibility to the drug over time could account for its increased effectiveness in the second part of the experiment. The experiment was de-

signed so that the occurrence of tachyphylaxis would have tended to decrease, rather than increase, the difference between drug and placebo. Therefore, an effort was made to minimize the effect of the fixed sequence of the experiment, and it is our belief that the results were not significantly biased by it.

Fisher *et al.*[5] suggested that greater response to drugs in association with expectation of therapeutic effect may not be due entirely to placebo effect; more important may be an increased sensitivity to expected drug effects engendered by an awareness of what the drug may do. This general hypothesis seems to be borne out by the data of this experiment, since the suggestion that an appetite-depressing drug might be given greatly enhanced the difference between drug and placebo. There are evident implications for this hypothesis in considering the use of rigid double-blind techniques for the evaluation of drugs which are designed to have mild effects on mood, thought, or behavior. These experiments suggest that drug effects of mild degree may be missed when patients or subjects have no preset framework in which to interpret subtle changes in their affect or bodily functions.

Summary and Conclusions

1. In 50 experiments with 4 subjects of normal weight, food intake and feelings of hunger were measured following the double-blind administration of phenmetrazine, 25 mg., or matching placebo in a randomized schedule.

2. In 28 experiments, subjects did not know what drug effects to expect, and phenmetrazine did not significantly reduce food intake.

3. In 22 experiments, subjects knew that an appetite-depressing drug might be given, and phenmetrazine significantly reduced food intake.

4. Expectation did not change subjective feelings of hunger, as measured by a simple checklist.

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Maurice Bouvet Prize Award

The 1964 Maurice Bouvet psychoanalytic prize has been awarded to Mlle. Anne Mermann for her translations into French of the work of Sigmund Freud.